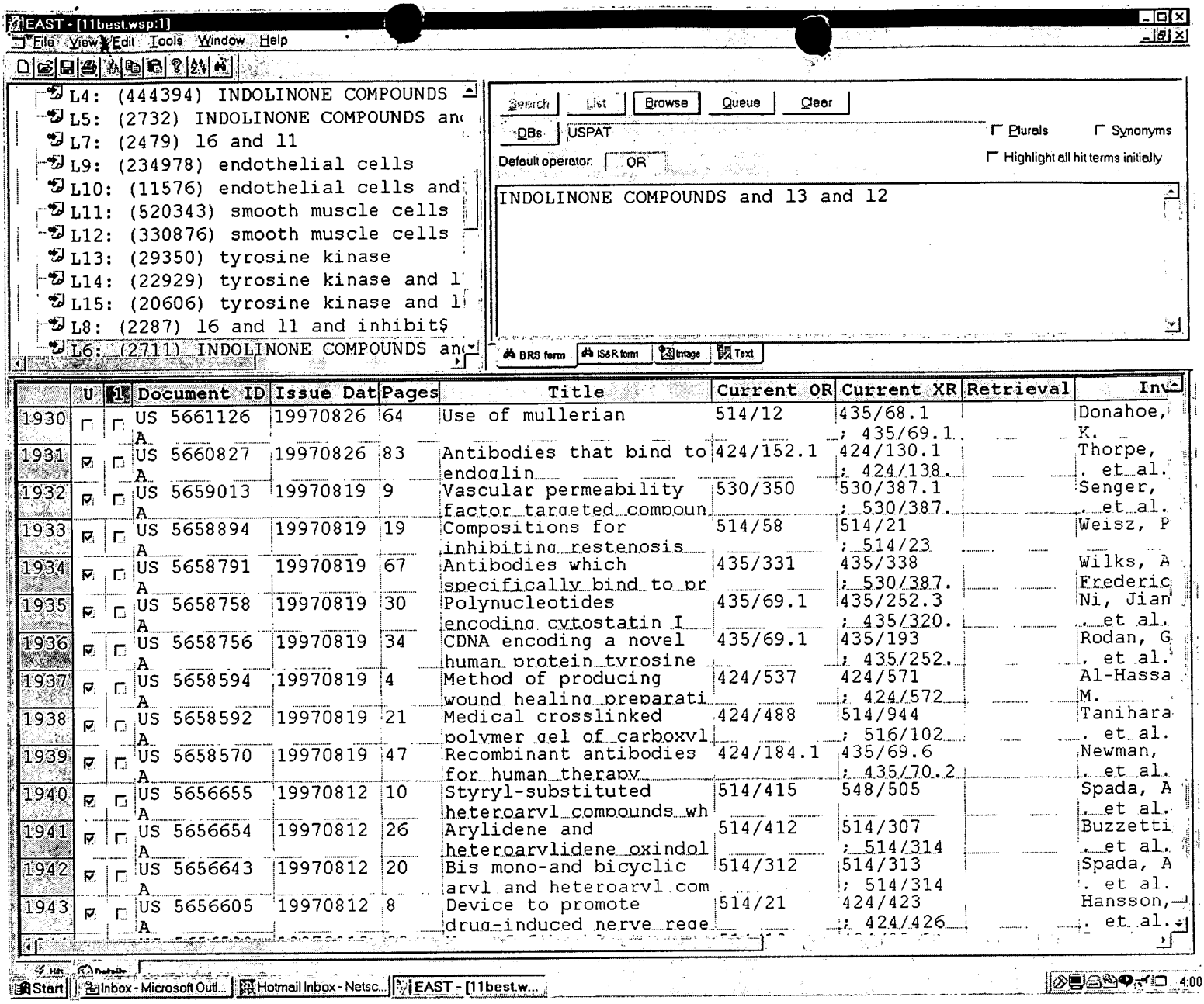


| | U | | Document ID | Issue Dat | Pages | Title | Current OR | Current XR | Retrieval | In |
|---|---|---|---|---|---|---|---|---|---|---|
| 1930 | ☐ | ☐ | US 5661126 A | 19970826 | 64 | Use of mullerian | 514/12 | 435/68.1 ; 435/69.1 | | Donahoe, K. |
| 1931 | ☑ | ☐ | US 5660827 A | 19970826 | 83 | Antibodies that bind to endoglin | 424/152.1 | 424/130.1 ; 424/138. | | Thorpe, . et al. |
| 1932 | ☑ | ☐ | US 5659013 A | 19970819 | 9 | Vascular permeability factor targeted compoun | 530/350 | 530/387.1 ; 530/387. | | Senger, . et al. |
| 1933 | ☑ | ☐ | US 5658894 A | 19970819 | 19 | Compositions for inhibiting restenosis | 514/58 | 514/21 ; 514/23 | | Weisz, P |
| 1934 | ☑ | ☐ | US 5658791 A | 19970819 | 67 | Antibodies which specifically bind to pr | 435/331 | 435/338 ; 530/387. | | Wilks, A Frederic |
| 1935 | ☑ | ☐ | US 5658758 A | 19970819 | 30 | Polynucleotides encoding cytostatin I | 435/69.1 | 435/252.3 ; 435/320. | | Ni, Jian . et al. |
| 1936 | ☑ | ☐ | US 5658756 A | 19970819 | 34 | CDNA encoding a novel human protein tyrosine | 435/69.1 | 435/193 ; 435/252. | | Rodan, G . et al. |
| 1937 | ☑ | ☐ | US 5658594 A | 19970819 | 4 | Method of producing wound healing preparati | 424/537 | 424/571 ; 424/572 | | Al-Hassa M. |
| 1938 | ☑ | ☐ | US 5658592 A | 19970819 | 21 | Medical crosslinked polymer gel of carboxyl | 424/488 | 514/944 ; 516/102 | | Tanihara . et al. |
| 1939 | ☑ | ☐ | US 5658570 A | 19970819 | 47 | Recombinant antibodies for human therapy | 424/184.1 | 435/69.6 ; 435/70.2 | | Newman, . et al. |
| 1940 | ☑ | ☐ | US 5656655 A | 19970812 | 10 | Styryl-substituted heteroaryl compounds wh | 514/415 | 548/505 | | Spada, A . et al. |
| 1941 | ☑ | ☐ | US 5656654 A | 19970812 | 26 | Arylidene and heteroarylidene oxindol | 514/412 | 514/307 ; 514/314 | | Buzzetti . et al. |
| 1942 | ☑ | ☐ | US 5656643 A | 19970812 | 20 | Bis mono-and bicyclic aryl and heteroaryl com | 514/312 | 514/313 ; 514/314 | | Spada, A . et al. |
| 1943 | ☑ | ☐ | US 5656605 A | 19970812 | 8 | Device to promote drug-induced nerve rege | 514/21 | 424/423 ; 424/426 | | Hansson, . et al. |

EAST - [11best.wsp:1]

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L4: (444394) INDOLINONE COMPOUNDS
L5: (2732) INDOLINONE COMPOUNDS an
L7: (2479) l6 and l1
L9: (234978) endothelial cells
L10: (11576) endothelial cells and
L11: (520343) smooth muscle cells
L12: (330876) smooth muscle cells
L13: (29350) tyrosine kinase
L14: (22929) tyrosine kinase and l
L15: (20606) tyrosine kinase and l
L8: (2287) l6 and l1 and inhibit$
L6: (2711) INDOLINONE COMPOUNDS an

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|---|---|---|---|---|---|---|---|---|---|---|
| 1970 | | ☑ | US 5650415 A | 19970722 | 23 | Quinoline compounds | 514/312 | 514/313 ; 546/153 | | Tang, Pe . et al. |
| 1971 | ☑ | | US 5650313 A | 19970722 | 32 | Ubiquitin conjugating enzymes 8 and 9 | 435/193 | 435/252.3 ; 435/320. | | Ni, Jian . et al. |
| 1972 | ☑ | | US 5650293 A | 19970722 | 35 | Nucleic acid encoding pp60.sup.PIK and the me | 435/69.1 | 435/252.3 ; 435/320. | | White, M |
| 1973 | ☑ | | US 5650267 A | 19970722 | 27 | Method of detecting compounds utilizing gen | 435/5 | 435/235.1 ; 435/320. | | Ray, Bry . et al. |
| 1974 | ☑ | | US 5650148 A | 19970722 | 114 | Method of grafting genetically modified ce | 424/93.2 | 424/93.21 ; 435/948 | | Gage, Fr . et al. |
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| 1977 | ☑ | | US 5648334 A | 19970715 | 42 | Methods of treatment using ciliary neurotrop | 514/12 | 514/2 ; 530/350 | | Davis, S . et al. |
| 1978 | ☑ | | US 5648217 A | 19970715 | 19 | DNA sequence which binds transcriptional r | 435/6 | 435/69.8 ; 435/7.1 | | Levy, Da |
| 1979 | ☑ | | US 5646261 A | 19970708 | 30 | 3'-derivatized oligonucleotide analogs | 536/24.3 | 536/24.5 | | Uhlmann, . et al. |
| 1980 | ☑ | | US 5646251 A | 19970708 | 39 | Alloreaction-associated antigen (ARAG): a novel | 530/350 | 435/69.1 ; 530/324 | | Ruegg, C . et al. |
| 1981 | ☑ | | US 5646153 A | 19970708 | 56 | Bis mono- and bicyclic aryl and heteroaryl com | 514/259 | 514/248 ; 514/249 | | Spada, A . et al. |
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| 1983 | ☑ | | US 5646109 A | 19970708 | 25 | Convertible microemulsion formulati | 514/2 | 424/400 ; 514/12 | | Owen, Al . et al. |

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NCBI PubMed National Library of Medicine NLM

PubMed Nucleotide Protein Genome Structure PopSet Taxonomy OMIM

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Blood. 1997 Sep 15;90(6):2253-9.

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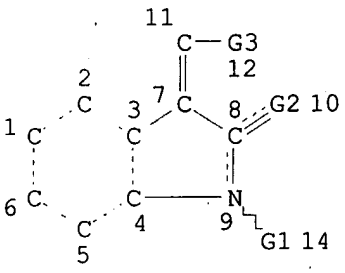
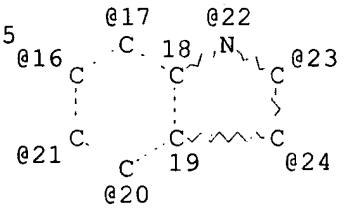



Ak @13

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Claim 2
A limited to thiophene, pyrrole, 4,5,6,7 tetrahydroindole

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RSPEC I
NUMBER OF NODES IS 25

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FILE 'HCAPLUS' ENTERED AT 09:47:15 ON 24 MAY 2001
L7 84 S L6
L8 21787 S VEGF OR PDGF OR FGF OR (VASCULAR ENDOTHELIAL OR PLATELET DERI
L9 64218 S PROLIFER? OR ANTIPROLIF?

FILE 'STNGUIDE' ENTERED AT 09:50:24 ON 24 MAY 2001

FILE 'HCAPLUS' ENTERED AT 09:58:32 ON 24 MAY 2001
L10 37 S L7 AND (L8 OR L9)
L11 8 S L7 AND L8 AND L9 claim 2 w/ keywords
L12 29 S L10 NOT L11
L13 7 S L12 AND (63/SC,SX OR PHARMA?) - claim other pharmaceut.

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L11 ANSWER 1 OF 8 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 2001:153502 HCAPLUS
TITLE: Inhibition of the **VEGF** receptor 2 combined with chronic hypoxia causes cell death-dependent pulmonary endothelial cell **proliferation** and severe pulmonary hypertension
AUTHOR(S): Taraseviciene-Stewart, Laimute; Kasahara, Yasunori; Alger, Lori; Hirth, Peter; McMahon, Gerald; Waltenberger, Johannes; Voelkel, Norbert F.; Tuder, Rubin M.
CORPORATE SOURCE: Department of Pathology, Division of Pulmonary Sciences and Critical Care Medicine, University of Colorado Health Sciences Center, Denver, CO, 80262, USA
SOURCE: FASEB J. (2001), 15(2), 427-438
CODEN: FAJOEC; ISSN: 0892-6638 -

PUBLISHER: Federation of American Societies for Experimental Biology
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Our understanding of the pathobiol. of severe pulmonary hypertension, usually a fatal disease, has been hampered by the lack of information of its natural history. We have demonstrated that, in human severe pulmonary hypertension, the precapillary pulmonary arteries show occlusion by proliferated endothelial cells. Vascular endothelial growth factor (VEGF) and its receptor 2 (VEGFR-2) are involved in proper maintenance, differentiation, and function of endothelial cells. We demonstrate here that VEGFR-2 blockade with SU5416 in combination with chronic hypobaric hypoxia causes severe pulmonary hypertension assocd. with precapillary arterial occlusion by proliferating endothelial cells. Prior to and concomitant with the development of severe pulmonary hypertension, lungs of chronically hypoxic SU5416-treated rats show significant pulmonary endothelial cell death, as demonstrated by activated caspase 3 immunostaining and TUNEL. The broad caspase inhibitor Z-Asp-CH2-DCB prevents the development of intravascular pulmonary endothelial cell growth and severe pulmonary hypertension caused by the combination of SU5416 and chronic hypoxia.

CC 14-5 (Mammalian Pathological Biochemistry)

ST VEGFR chronic hypoxia pulmonary hypertension artery cell **proliferation**

IT Proteins, specific or class
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(Akt; VEGFR-2 blockade with SU5416 in combination with chronic hypobaric hypoxia causes severe pulmonary hypertension assocd. with precapillary arterial occlusion by **proliferating** endothelial cells)

IT Transcription factors
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(Src; VEGFR-2 blockade with SU5416 in combination with chronic hypobaric hypoxia causes severe pulmonary hypertension assocd. with precapillary arterial occlusion by **proliferating** endothelial cells)

IT Apoptosis
Cell death
Cell **proliferation**
Lung
(VEGFR-2 blockade with SU5416 in combination with chronic hypobaric hypoxia causes severe pulmonary hypertension assocd. with precapillary arterial occlusion by **proliferating** endothelial cells)

IT Hypoxia, animal
(chronic; VEGFR-2 blockade with SU5416 in combination with chronic hypobaric hypoxia causes severe pulmonary hypertension assocd. with precapillary arterial occlusion by **proliferating** endothelial cells)

IT **Vascular endothelial growth factor** receptors
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(gene KDR; VEGFR-2 blockade with SU5416 in combination with chronic hypobaric hypoxia causes severe pulmonary hypertension assocd. with precapillary arterial occlusion by **proliferating** endothelial cells)

IT Artery
(pulmonary, endothelium; VEGFR-2 blockade with SU5416 in combination with chronic hypobaric hypoxia causes severe pulmonary hypertension assocd. with precapillary arterial occlusion by **proliferating** endothelial cells)

IT Hypertension
(pulmonary; VEGFR-2 blockade with SU5416 in combination with chronic hypobaric hypoxia causes severe pulmonary hypertension assocd. with precapillary arterial occlusion by **proliferating** endothelial cells)

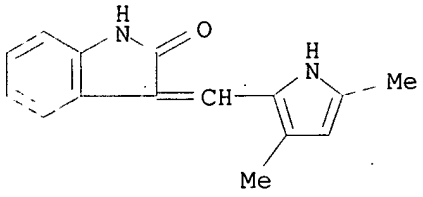
IT **204005-46-9**, SU5416
RL: BAC (Biological activity or effector, except adverse); BIOL (Biological study)
(VEGFR-2 blockade with SU5416 in combination with chronic hypobaric hypoxia causes severe pulmonary hypertension assocd. with precapillary arterial occlusion by **proliferating** endothelial cells)

IT 169592-56-7, caspase 3
RL: BOC (Biological occurrence); BIOL (Biological study); OCCU (Occurrence)
(VEGFR-2 blockade with SU5416 in combination with chronic hypobaric hypoxia causes severe pulmonary hypertension assocd. with precapillary arterial occlusion by **proliferating** endothelial cells)

IT **204005-46-9**, SU5416
RL: BAC (Biological activity or effector, except adverse); BIOL (Biological study)
(VEGFR-2 blockade with SU5416 in combination with chronic hypobaric hypoxia causes severe pulmonary hypertension assocd. with precapillary arterial occlusion by **proliferating** endothelial cells)

RN 204005-46-9 HCAPLUS

CN 2H-Indol-2-one, 3-[(3,5-dimethyl-1H-pyrrol-2-yl)methylene]-1,3-dihydro- (9CI) (CA INDEX NAME)




REFERENCE COUNT: 32

REFERENCE(S):
(1) Alon, T; Nature Med 1995, V1, P1024 HCAPLUS
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(4) Daemen, M; J Clin Invest 1999, V104, P541 HCAPLUS
(5) Dimmeler, S; Cell Death Differ 1999, V6, P964 HCAPLUS
(6) Feng, Y; Biochem Biophys Res Commun 1999, V256, P192 HCAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 2 OF 8 HCAPLUS COPYRIGHT 2001 ACS

ACCESSION NUMBER: 2000:417312 HCAPLUS

DOCUMENT NUMBER: 133:159618

TITLE: Identification of Substituted 3-[(4,5,6,7-Tetrahydro-1H-indol-2-yl)methylene]-1,3-dihydroindol-2-ones as

Growth Factor Receptor Inhibitors for **VEGF**-R2 (Flk-1/KDR), **FGF**-R1, and **PDGF**-R.beta. Tyrosine Kinases

AUTHOR(S): Sun, Li; Tran, Ngoc; Liang, Congxing; Hubbard, Steve; Tahg, Flora; Lipson, Kenneth; Schreck, Randall; Zhou, Yong; McMahon, Gerald; Tang, Cho

CORPORATE SOURCE: SUGEN Inc., South San Francisco, CA, 94080-4811, USA

SOURCE: J. Med. Chem. (2000), 43(14), 2655-2663
CODEN: JMCMAR; ISSN: 0022-2623

PUBLISHER: American Chemical Society

DOCUMENT TYPE: Journal

LANGUAGE: English

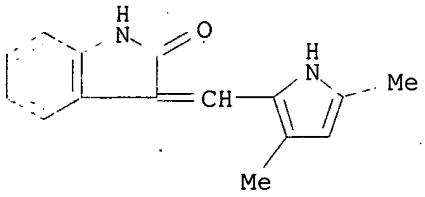
AB A series of new 3-substituted indolin-2-ones contg. a tetrahydroindole moiety was developed as specific inhibitors of receptor tyrosine kinases assocd. with VEGF-R, FGF-R, and PDGF-R growth factor receptors. These compds. were evaluated for their inhibitory properties toward VEGF-R2 (Flk-1/KDR), FGF-R1, PDGF-R.beta., p60c-Src, and EGF-R tyrosine kinases and their ability to inhibit growth factor-dependent cell proliferation. Structure-activity relationships of this new pharmacophore have been detd. at the level of kinase inhibition. Compds. contg. a propionic acid moiety at the C-3' position of the tetrahydroindole ring represented the most potent indolin-2-ones to inactivate the VEGF, FGF, and PDGF receptor kinases. The inhibitory activities of 3-[3-(2-carboxyethyl)-4,5,6,7-tetrahydro-1H-indol-2-ylmethylene]-2-oxo-2,3-dihydro-1H-indole-5-carboxylic acid against VEGF-R2 (Flk-1), 3-{2-[6-(2-methoxyphenyl)-2-oxo-1,2-dihydroindol-3-ylidenemethyl]-4,5,6,7-tetrahydro-1H-indol-3-yl}propionic acid against FGF-R1, and 3-[2-(5-bromo-2-oxo-1,2-dihydroindol-3-ylidenemethyl)-4,5,6,7-tetrahydro-1H-indol-3-yl]propionic acid (I) against PDGF-R.beta. were 4, 80, and 4 nM, resp. However, all of these compds. were inactive when tested against the EGF-R tyrosine kinase. Compds. 3-[2-(2-oxo-1,2-dihydroindol-3-ylidenemethyl)-4,5,6,7-tetrahydro-1H-indol-3-yl]propionic acid (II) and I represented the most potent inhibitors of these classes to inhibit both biochem. kinase and growth factor-dependent cell proliferation for these three targets. In addn., compd. II was cocrystd. with the catalytic domain of FGF-R1 providing evidence to explain the structure-activity relation results. This study has provided evidence to support the potential of these new tyrosine kinase inhibitors for the treatment of angiogenesis and other growth factor-related diseases including human cancers.

CC 1-3 (Pharmacology)
Section cross-reference(s): 2, 7, 27, 75

IT Enzyme functional sites
(active; substituted [(tetrahydroindolyl)methylene]dihydroindolones as growth factor receptor inhibitors for **VEGF**-R2 (Flk-1/KDR) and **FGF**-R1, and **PDGF**-R.beta. tyrosine kinases and as inhibitors of growth factor-dependent cell **proliferation**)

IT **Vascular endothelial growth factor** receptors
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(gene KDR; substituted [(tetrahydroindolyl)methylene]dihydroindolones as growth factor receptor inhibitors for **VEGF**-R2 (Flk-1/KDR) and **FGF**-R1, and **PDGF**-R.beta. tyrosine kinases and as inhibitors of growth factor-dependent cell **proliferation**)

IT Structure-activity relationship



=> d .ca l13 1-7

L13 ANSWER 1 OF 7 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 2000:456819 HCAPLUS
DOCUMENT NUMBER: 133:84238
TITLE: 3-heteroarylidenyl-2-indolinone compounds for modulating protein kinase activity and for use in cancer chemotherapy
INVENTOR(S): Langecker, Peter J.; Shawver, Laura Kay; Tang, Peng Cho; Sun, Li
PATENT ASSIGNEE(S): Sugen, Inc., USA
SOURCE: PCT Int. Appl., 148 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
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| WO 2000038519 | A1 | 20000706 | WO 1999-US31232 | 19991230 |

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RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 1998-114313 P 19981231
OTHER SOURCE(S): MARPAT 133:84238
AB 3-Heteroarylidenyl-2-indolinone compds. are provided that modulate the enzymic activity of protein kinases and therefore are expected to be useful in the prevention and treatment of protein kinase-related cellular disorders, e.g. cancer. Furthermore, these compds. are expected to enhance the efficacy of other chemotherapeutic agents, in particular, fluorinated pyrimidines, in the treatment of cancer.
IC ICM A01N043-38
ICS A61K031-40
CC 1-6 (Pharmacology)
Section cross-reference(s): 27, **63**
IT Cell **proliferation**
Kidney, neoplasm

PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
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| WO 9640116 | A1 | 19961219 | WO 1996-US8903 | 19960605 |
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| RW: KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG | | | | |
| US 5880141 | A | 19990309 | US 1995-485323 | 19950607 |
| CA 2192797 | AA | 19961219 | CA 1996-2192797 | 19960605 |
| AU 9660441 | A1 | 19961230 | AU 1996-60441 | 19960605 |
| AU 706597 | B2 | 19990617 | | |
| EP 769947 | A1 | 19970502 | EP 1996-918093 | 19960605 |
| EP 769947 | B1 | 20010502 | | |
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| BR 9606410 | A | 19971230 | BR 1996-6410 | 19960605 |
| JP 10504323 | T2 | 19980428 | JP 1996-501363 | 19960605 |
| EP 934931 | A2 | 19990811 | EP 1999-103667 | 19960605 |
| EP 934931 | A3 | 19991020 | | |
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| JP 2000026412 | A2 | 20000125 | JP 1999-159567 | 19960605 |
| NO 9605377 | A | 19970212 | NO 1996-5377 | 19961213 |

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| | EP 1996-918093 | A3 | 19960605 |
| | JP 1997-501363 | A3 | 19960605 |
| | WO 1996-US8903 | W | 19960605 |

OTHER SOURCE(S): MARPAT 126:139901

AB The present invention relates to org. mols. capable of modulating tyrosine kinase signal transduction in order to regulate, modulate and/or inhibit abnormal cell proliferation. Representatives of the 5 different classes of compds. described are SU 4932 [3-(2-chloro-4-hydroxybenzylidenyl)-2-indolinone], SU 4312 [3-(4-dimethylaminobenzylidenyl)-2-indolinone], SU 5416 {3-[(2,4-dimethylpyrrol-5-yl)methylene]-2-indolinone}, SU 5204 [3-(2-ethoxybenzylidenyl)-2-indolinone], and SU 4942 [3-(4-bromobenzylidenyl)-2-indolinone]. Diseases which these compds. and their pharmaceutically acceptable prepns. may be effective against include arthritis, hepatic cirrhosis, diabetic nephropathy and psoriasis.

IC ICM A61K031-40
ICS C07C209-34

CC 1-12 (Pharmacology)
Section cross-reference(s): 27, 63

IT Epidermal growth factor receptors
**Fibroblast growth factor** receptors
Insulin receptors
Insulin-like growth factor I receptors
**Platelet-derived growth factor** receptors
RL: BSU (Biological study, unclassified); BIOL (Biological study) (prepn. of indolinones capable of modulating tyrosine kinase signal transduction)

L13 ANSWER 7 OF 7 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1997:640690 HCAPLUS
DOCUMENT NUMBER: 127:314804
TITLE: Assays for KDR/FLK-1 receptor tyrosine kinase inhibitors, and use of the inhibitors for treatment of vasculogenesis- and angiogenesis-related diseases
INVENTOR(S): Hirth, Klaus P.; McMahon, Gerald; Shawver, Laura K.
PATENT ASSIGNEE(S): Sugen, Inc., USA
SOURCE: PCT Int. Appl., 65 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 9734920 | A1 | 19970925 | WO 1997-US3378 | 19970304 |
| W: AL, AM, AU, AZ, BA, BB, BG, BR, BY, CA, CN, CU, CZ, EE, GE, GH, HU, IL, IS, JP, KG, KP, KR, KZ, LC, LK, LR, LT, LV, MD, MG, MK, MN, MX, NO, NZ, PL, RO, RU, SG, SI, SK, TJ, TM, TR, TT, UA, UZ, VN, YU, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM | | | | |
| RW: GH, KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG | | | | |
| AU 9720667 | A1 | 19971010 | AU 1997-20667 | 19970304 |
| PRIORITY APPLN. INFO.: | | | US 1996-621734 | 19960321 |
| | | | WO 1997-US3378 | 19970304 |

AB Processes are disclosed for the identification of compds. and pharmaceutical compns. capable of selectively and potently inhibiting KDR/FLK-1 tyrosine kinase signal transduction in order to inhibit vasculogenesis and/or angiogenesis. The invention also relates to compds. and compns. identified using the methods of the invention and the use thereof for the treatment of disease relating to inappropriate vasculogenesis and/or angiogenesis. The invention provides an assay cascade comprised of several "filter steps" of increasing selectivity which identify a limited subset of candidate compds. affecting the VEGF receptor on the mol. level.

IC ICM C07K002-00
ICS C07K014-705; C07K016-28; C12N005-06; C12N005-07; C12Q001-00; A16K031-00; A16K035-00; A16K039-395; G01N033-15; G01N033-48; G01N022-53

CC 1-1 (Pharmacology)
Section cross-reference(s): **63**

IT Animal cell line
(EPH-4/**VEGF**; KDR/FLK-1 receptor tyrosine kinase inhibitor identification assay, and use of compds. for treatment of vasculogenesis- and angiogenesis-related diseases)

IT Antibodies
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(immobilized, to **VEGF** receptor; KDR/FLK-1 receptor tyrosine kinase inhibitor identification assay, and use of compds. for treatment of vasculogenesis- and angiogenesis-related diseases)

IT Growth factor receptors

RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(**vascular endothelial growth factor**, gene KDR; KDR/FLK-1 receptor tyrosine kinase inhibitor identification assay, and use of compds. for treatment of vasculogenesis- and angiogenesis-related diseases)

IT Growth factor receptors
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(**vascular endothelial growth factor**, gene flt 1; KDR/FLK-1 receptor tyrosine kinase inhibitor identification assay, and use of compds. for treatment of vasculogenesis- and angiogenesis-related diseases)

IT Receptors
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(**vascular endothelial growth factor**; KDR/FLK-1 receptor tyrosine kinase inhibitor identification assay, and use of compds. for treatment of vasculogenesis- and angiogenesis-related diseases)

IT 127464-60-2, **Vascular endothelial growth factor**
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BIOL (Biological study); PROC (Process)
(KDR/FLK-1 receptor tyrosine kinase inhibitor identification assay, and use of compds. for treatment of vasculogenesis- and angiogenesis-related diseases)

IT 3359-49-7, SU 4928 5812-07-7, SU 4312 **62540-08-3**, SU 5208 **91822-51-4**, SU 4314 186611-03-0, SU 4932 186611-55-2, SU 4313 197592-54-4, SU 0879 197592-55-5, SU 1076 197592-56-6, SU 1385 197592-57-7, SU 1387 197592-58-8, SU 1393 197592-59-9, SU 1433 197592-60-2, SU 1498 197592-61-3, SU 1835 197592-62-4, SU 4136 197592-63-5, SU 4157 197592-64-6, SU 4161 197592-65-7, SU 4209 197592-66-8, SU 4304 197592-67-9, SU 4328 197592-68-0, SU 4334 197592-69-1, SU 4348 197592-70-4, SU 4929 197592-71-5, SU 4936 197592-72-6, SU 4943 197592-73-7, SU 4945 197592-74-8, SU 5014 197592-75-9, SU 5015 **204005-46-9**, SU 5416
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(KDR/FLK-1 receptor tyrosine kinase inhibitor identification assay, and use of compds. for treatment of vasculogenesis- and angiogenesis-related diseases)

IT 141350-03-0, Flt-1 **VEGF** receptor tyrosine kinase 150977-45-0, Flk-1/KDR **VEGF** receptor tyrosine kinase
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(KDR/FLK-1 receptor tyrosine kinase inhibitor identification assay, and use of compds. for treatment of vasculogenesis- and angiogenesis-related diseases)

Congxin; Schlessinger, Joseph; Hubbard, Stevan R.; McMahon, Gerald; Tang, Peng C.
SOURCE: PCT Int. Appl., 493 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 9807835 | A2 | 19980226 | WO 1997-US14885 | 19970821 |
| WO 9807835 | A3 | 19981001 | | |
| W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM | | | | |
| RW: GH, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG | | | | |
| US 5942428 | A | 19990824 | US 1996-701191 | 19960821 |
| AU 9741603 | A1 | 19980306 | AU 1997-41603 | 19970821 |
| EP 931152 | A2 | 19990728 | EP 1997-939534 | 19970821 |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI | | | | |

PRIORITY APPLN. INFO.: US 1996-701191 19960821
US 1996-34168 19961219
WO 1997-US14885 19970821
OTHER SOURCE(S): MARPAT 128:164361

AB The present invention relates to the 3-dimensional structures of a protein tyrosine kinase optionally complexed with one or more compds. Thus, a 310-amino acid fragment fibroblast growth factor receptor 1 (residues 456-765, FGFR1) was recombinantly prepd. contg. the amino acid substitutions Cys488.fwdarw.Ala, Cys584.fwdarw.Ser, and Leu457.fwdarw.Val, and an addnl. 5 residues (Ser-Ala-Ala-Gly-Thr) at the N-terminus. X-ray crystallog. yielded the at. structural coordinates of cryst. FGFR1 and its complexes with adenylyl diphosphonate, 3-[(3-(2-carboxyethyl)-4-methylpyrrol-5-yl)methylene]-2-indolinone, or 3-[4-(4-formylpiperazine-1-yl)benzylidenyl]-2-indolinone. Two forms of cryst. FGFR1 were obtained: one form (designated C2-A form) with unit cell dimensions of a = 208.3, b = 57.2, c = 65.5.ANG. and .beta. = 107.2.degree., and another C2-B form with dimensions a = 211.6, b = 51.3, c = 66.1.ANG. and .beta. = 107.7.degree.. The overall structure of FGFR1 is bi-lobate. The N-terminal lobe of FGFR1 spans amino acid residues 456-567 and comprises a curled .beta.-sheet of five antiparallel strands and one .alpha.-helix. The C-terminal lobe spans amino acid residues 568-765 and comprises two .beta.-strands and seven .alpha.-helixes. The at. coordinates that define the structures of the protein tyrosine kinase and any of the compds. bound to it are pertinent to methods for detg. the 3-dimensional structures of protein tyrosine kinases with unknown structure and to methods that

FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 9948868 | A2 | 19990930 | WO 1999-US6468 | 19990326 |
| WO 9948868 | A3 | 20000224 | | |
| W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM | | | | |
| RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG | | | | |
| AU 9933635 | A1 | 19991018 | AU 1999-33635 | 19990326 |
| EP 1066257 | A2 | 20010110 | EP 1999-915018 | 19990326 |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI | | | | |

PRIORITY APPLN. INFO.:

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|---|---|---|
| US 1998-79713 | P | 19980326 |
| US 1998-80422 | P | 19980402 |
| US 1998-81792 | P | 19980415 |
| US 1998-82056 | P | 19980416 |
| US 1998-89397 | P | 19980615 |
| US 1998-89521 | P | 19980616 |
| US 1998-98783 | P | 19980901 |
| WO 1999-US6468 | W | 19990326 |

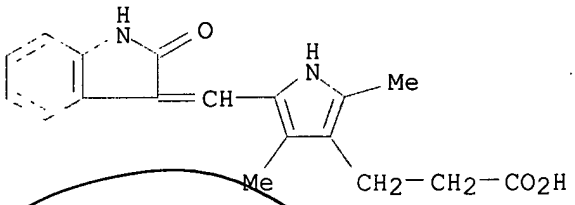
OTHER SOURCE(S): MARPAT 131:257441

AB The invention relates to certain indolinone-based and pyrazolylamide-based compds., I and II, their method of synthesis, and combinatorial libraries consisting of the compds. [wherein AB = atoms to make up 1-2 fused and/or connected rings; R = arom. or heteroarom. ring which may form an addnl. ring by cyclization to the methylene group; R1, R2 = H, alkyl, (hetero)aryl or -aliph. ring, amino, NO2, halo, etc.; R3 = (un)substituted Ph; Z = (un)substituted (CH2)0-3; R4, R5 = H, alkyl, (hetero)aryl or -aliph., amine, ketone, etc.]. The invention also relates to methods of modulating the function of protein kinases using these compds., and methods of treating diseases by modulating the function of protein kinases and related signal transduction pathways. Data for prepns. and/or biol. activity are given, as well as the prepns. of various oxindole intermediates. For instance, the pyrazolecarboxamide deriv. III gave up to 70% inhibition of growth of Calu-6 human lung carcinoma cells as a xenograft in mice. As another example, the indolinone deriv. IV was prepd. by condensation of 6-(4-methoxyphenyl)-2-oxindole with 3,5-dimethyl-1H-pyrrole-2-carboxaldehyde in the presence of piperidine. Extensive tests of a few selected compds. against a variety of protein kinases are described.

IC ICM C07D209-34
ICS C07D403-06; C07D409-06; A61K031-40; A61K031-415

CC 27-11 (Heterocyclic Compounds (One Hetero Atom))
Section cross-reference(s): 1

IT Blood vessel
(endothelium, inhibition of **proliferation**; prepn. of pyrazolecarboxylic acid amides and (arylmethylene)indolinones as



L11 ANSWER 7 OF 8 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1998:147306 HCAPLUS
DOCUMENT NUMBER: 128:204803
TITLE: Indolinone combinatorial libraries and related products and methods for the treatment of disease
INVENTOR(S): Tang, Peng Cho; Sun, Li; McMahon, Gerald; Hirth, Klaus Peter; Shawver, Laura Kay; et al.
PATENT ASSIGNEE(S): Sugen, Inc., USA; Tang, Peng Cho; Sun, Li; McMahon, Gerald
SOURCE: PCT Int. Appl., 293 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 9807695 | A1 | 19980226 | WO 1997-US14736 | 19970820 |
| W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM | | | | |
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| CN 1155838 | A | 19970730 | CN 1996-190616 | 19960605 |
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